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EXAMINER	
BALLARD, KIMBERLY A	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 08/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/777,792	SCHENK ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-143* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Election/Restrictions

Applicant's election without traverse of Group I, original claims 69-78 and 102-103 drawn to a chimeric peptide comprising Aβ and a T-helper cell epitope, in the reply filed on 02 June 2006 is acknowledged.

In the amendment filed 02 June 2006, Applicant has cancelled claims 1-118 and has added new claims 119-143, which are directed to a pharmaceutical composition comprising Aβ1-7 linked to CRM197, and drawn to the originally elected invention of Group I. In view of the claim amendments, the species election of the Restriction Requirement of 2 March 2006 is rendered moot.

Claims **119-143** are pending and under examination in the current office action.

Information Disclosure Statement

A signed and initialed copy of the IDS paper submitted 19 August 2006 is enclosed in this action.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos. 09/322,289, 09/201,430 (now US Patent No. 6,787,523), and 60/080,970, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Literal support for the claim limitation "Aβ1-7" is not demonstrated in any of the above listed applications. Support for the instantly recited claim limitation of "Aβ1-7" is first documented in Application No. 09/580,018 (now US Patent No. 6,761,888), filed 26 May 2000. Accordingly, for purposes of prior art, the effective filing date of instant claims 119-143 is **26 May 2000**.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 131-143 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 131 recites, "A pharmaceutical composition comprising Aβ1-7 linked to CRM197 to form a conjugate and an adjuvant". The claim as written is indefinite and ambiguous because it is unclear whether the composition comprises the two substances, that is, an adjuvant and Aβ1-7/CRM197, or whether the linkage of Aβ1-7 to CRM197 produces a composition that is both a conjugate *and* an adjuvant. Appropriate correction is required. Claims 132-143 are similarly rejected as they depend from claim 131.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 119, 121-124, 126-131, 134-137, and 139-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/42306 A2 by Chain (as listed on Applicant's IDS), published 14 June 2001 (priority date: 8 December 1999), as evidenced by Alberts et al. (Molecular Biology of the Cell, 2nd Edn. Garland Publishing, New York, 1989, pp. 266-267), and in view of Frenkel et al. (*J Neuroimmunology*, March 1999; **95**: 136-142), US Patent No. 5,601,827 to Collier et al., issued 11 February 1997, and Van den Dobbelsteen et al. (*Scand J. Immunol*, 1995; **41**: 273-280).

The claims are directed to a pharmaceutical composition comprising Aβ1-7 linked to CRM197 to form a conjugate, or a composition comprising an adjuvant and said conjugate (claims 119 and 131). Noted claim limitations include: the composition comprises at least 10, 20, 50, or 100 μg of Aβ1-7 (claims 121-124 and 134-137); wherein Aβ1-7 is linked to CRM197 at the amino or carboxyl terminus (claims 126, 127, 129, 130, 139, 140, 142, and 143); and wherein the conjugate is expressed as a fusion protein (claims 128 and 141).

In WO 01/42306 A2, Chain teaches a chimeric peptide or mixture of chimeric peptides that can be formulated as an immunizing composition and used in a method of immunization in a mammal against an internal peptide cleavage product derived from a

precursor or mature protein (see Abstract). Chain teaches that immunizing compositions are directed against the free N-terminus or C-terminus of the chimeric peptide, and that the chimeric peptide preferably is an amyloid-β (Aβ) peptide (see p. 9, lines 4-17). The chimeric peptide is taught to comprise a B cell epitope, such as the free N-terminus or free C-terminus of an Aβ peptide, fused with or without spacer amino acid residues to a strong T helper cell epitope (see p. 10, lines 7-17). The peptide may be linked to the T helper epitope at either the amino- or carboxyl-terminus of the peptide (see paragraph spanning p. 12, line 35 to p. 13, line 16). Such T helper cell epitopes include, for example, diphtheria toxin, tetanus toxin, and pertussis toxin, among others (p. 17, lines 16-27). Chain teaches that immunogenicity can also be significantly improved if the antigens are co-administered with adjuvants, such as saponins (p. 21, lines 5-6 and 31-33). Various amyloid-β peptides for use in the chimeric peptide are also encompassed by the invention (p. 14, lines 7-21). Chain also teaches that longer chimeric peptides can be synthesized by well-known recombinant DNA techniques (p. 19, lines 19-34). Although Chain does not explicitly use the phrase "fusion protein", one of skill in the art would recognize that the recombinant techniques disclosed by Chain to express the chimeric peptide via suitable host define the production of a fusion protein, as evidenced by Alberts et al. at p. 266. Finally, Chain discloses that the immunizing compositions in unit dosage form can contain about 0.5 μg to about 1 mg of each peptide per kg body weight (see p. 24, lines 11-15). Considering that the average human is approximately 70 kg, the dosages of the immunizing Aβ peptides disclosed by

Chain would equal about 70 μg to about 70 mg, which would meet the limitations recited in instant claims 121-124 and 134-137 of at least 10, 20, 50, or 100 μg of Aβ1-7 peptide.

However, Chain does not teach that the peptide is Aβ1-7, or that the peptide is linked to the specific diphtheria toxin CRM197.

Frenkel et al. teach the sequence DAEFRHD, which corresponds to Aβ1-7 (see Abstract, p. 136, and p. 139, 2nd column). Frenkel teaches that Aβ protein that adopts a β-sheet conformation is likely to lead to peptide aggregation, and is a proposed mechanism of plaque formation in Alzheimer's disease (see p. 136, 1st paragraph). Frenkel teaches that certain sequences within proteins may be involved in folding and conformational stabilization of the protein, and antibodies that interact at such folding sites may help to stabilize the protein and prevent further precipitation (see p. 136, 2nd paragraph). The Aβ1-7 peptide comprises the amino acid residues EFRH (Aβ3-6), which has been demonstrated to be an important epitope for site-directed monoclonal antibodies (mAbs) capable of binding to Aβ fibrils, leading to disaggregation of the fibrils and inhibition of their neurotoxic effects (see p. 140, 2nd column). Hence, the residues of Aβ1-7 encompass an important site within the N-terminus of the amyloid-β peptide for the generation of antibodies capable of inhibiting Aβ aggregation and plaque formation.

The teachings of Collier et al. in US 5,601,827 and Van den Dobbelsteen et al. are largely cumulative regarding the use of diphtheria toxin in vaccines. Collier et al. disclose the use vaccines comprising diphtheria toxin coupled to a moiety, such as a polysaccharide or second polypeptide, wherein the diphtheria toxoid polypeptide serves as a carrier substance for the moiety to enhance the immunogenicity of the moiety (see

column 4, lines 48-56). Collier et al. additionally teach that the diphtheria toxoid can be part of a fusion polypeptide consisting of the diphtheria toxoid linked by a peptide bond to an additional polypeptide (column 4, lines 57-60). Van den Dobelsteen et al. compare the immune response to a polysaccharide (pneumococcal polysaccharide type 14, PPS-14) alone versus PPS-14 conjugated to CRM-197 (a non-toxic mutant of diphtheria toxoid; CRM standing for "cross-reacting material"). Van den Dobbelsteen teaches that conjugation of PPS-14 to CRM-197 induced a significantly enhanced immune response compared to PPS-14 alone, wherein an enhancement of serum titres for IgM and IgG and an increase in the number of antibody-secreting cells was found (see p. 273, Abstract; and Figure 1 on p. 275).

It would have been obvious to one of skill in the art at the time the invention was made to modify the chimeric Aβ peptides taught by Chain et al. by conjugating the Aβ1-7 peptide taught by Frenkel et al. to CRM-197 diphtheria toxin, as taught by Collier et al. and Van den Dobbelsteen et al., either alone as a immunizing composition or in conjunction with an adjuvant in order to enhance the immune response to the Aβ peptide. Specifically, the artisan would be motivated to use Aβ1-7 because Frenkel teaches that this region comprises an epitope particularly important for inhibiting the fibrillogenic and neurotoxic properties of the Aβ peptide. The skilled artisan would likewise be motivated to conjugate the Aβ peptide to CRM-197 because both Chain et al. and Collier et al. teach that conjugation to a diphtheria toxin can enhance the immunogenicity of a peptide, and Van den Dobbelsteen teaches that CRM-197 is a non-toxic diphtheria toxoid that significantly enhances the immune response to a conjugated

moiety. Accordingly, the artisan would be motivated to produce Aβ1-7/CRM197 conjugates, administered with or without an adjuvant, not only to promote the production of anti-amyloidogenic antibodies which are recognized in the art for their anti-fibrillogenic properties, but also for the peptides demonstrated ability to attenuate Alzheimer's disease-like pathology in PDAPP mice serving as an animal model for Aβ deposition and Alzheimer's disease-like neuropathologies (see Chain et al., p. 6, lines 21-31). Such combination would be met with an expectation of success by the artisan based upon the numerous teachings within the references demonstrating the enhancement of immunogenic responses to toxin-conjugated peptides, particularly if combined with an adjuvant, to elicit anti-peptide antibodies. Thus, the combined references render the claimed invention obvious to the artisan at the time the invention was made.

Claims 120 and 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/42306 A2 by Chain, as evidenced by Alberts et al., and in view of Frenkel et al., US Patent No. 5,601,827 to Collier et al., and Van den Dobbelsteen et al., as applied to claims 119, 121-124, 126-131, 134-137, and 139-143 above, and further in view of US Patent Nos. 5,837,268 to Potter et al. (17 November 1998) and 5,733,548 to Restifo et al. (31 March 1998).

The claims are directed to a pharmaceutical composition comprising Aβ1-7 linked to CRM197 to form a conjugate, or a composition comprising an adjuvant and said conjugate, wherein the conjugate comprises a plurality of additional copies of Aβ1-7.

The teachings of the above combined references are discussed above, however, they do not teach the use of a plurality of additional copies of Aβ1-7 in the conjugate.

The teachings of Potter et al. and Restifo et al. are cumulative. Potter et al. notes that the art generally recognizes that the immunogenicity of viral antigens, small proteins or endogenous substances may be significantly increased by producing immunogenic forms of those molecules comprising multiple copies of selected epitopes (paragraph spanning column 1 – column 2, line 3). Restifo et al. teach immunogenic chimeric proteins used *in vivo* to elicit specific T cell responses (see column 2, lines 53-57). Restifo discloses that multiple copies of a peptide, which may or may not be immunogenic by itself, may be contained within the immunogenic chimeric protein (see column 4, lines 32-36, and column 5, lines 15-22).

Thus, it would have been obvious to one of skill in the art at the time the invention was made to modify the chimeric Aβ1-7 peptide linked to CRM-197, as discussed above, by inserting multiple copies of Aβ1-7 within the chimeric peptide conjugate. The artisan would be motivated to make such a modification because both Potter and Restifo teach that the immunogenicity of a small endogenous protein can be enhanced by including multiple copies of such a peptide within the immunogenic chimeric protein. The peptide Aβ1-7 is a small, endogenous protein and would not be predicted to be particularly immunogenic when administered by itself. The skilled artisan would therefore reasonably expect that including multiple copies of Aβ1-7 within the Aβ1-7/CRM-197 conjugate would enhance the immunogenic response when the chimeric peptide is administered as a pharmaceutical composition. Thus, the combined

references render the claimed invention obvious to the artisan at the time the invention was made.

Claims 125 and 138 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/42306 A2 by Chain, as evidenced by Alberts et al., and in view of Frenkel et al., US Patent No. 5,601,827 to Collier et al., and Van den Dobbelsteen et al., as applied to claims 119, 121-124, 126-131, 134-137, and 139-143 above, and further in view of Peeters et al. (*J Immunol Methods*, 1989; **120**(1): 133-143).

The claims are directed to a pharmaceutical composition comprising Aβ1-7 linked to CRM197 to form a conjugate, or a composition comprising an adjuvant and said conjugate, wherein Aβ1-7 is linked to CRM197 by chemical crosslinking.

The teachings of the above combined references are discussed above, however, they do not teach linking Aβ1-7 to CRM197 via chemical crosslinking.

Peeters et al. compare the effects of four different cross-linking reagents on the immunogenicity of peptide-carrier conjugates used to raise anti-peptide antibodies. The four reagents studied included three of the "maleimide" type: succinimidyl 6-(*N*-maleimido)-*n*-hexanoate (MHS), succinimidyl 4-(*N*-maleimidomethyl)-cyclohexane-1-carboxylate (SMCC), and succinimidyl m-maleimidobenoate (MBS). Also studied was a coupling reagent containing an activated disulphide: succinimidyl 3-(2-pyridyldithio)propionate (SPDP) (see Abstract, p. 133). Peeters et al. note that in order to induce immunogenicity, peptides which do not generally elicit antibody production are coupled to macromolecular carriers (see paragraph spanning p. 133-135). Conjugation

of peptides to other proteins by traditional methods can result in a great number of different products (i.e., "chaos" coupling; p. 135, 1st column). In order to obtain the best-defined product, Peeters notes, heterobifunctional cross-linkers should be used in such a way that the peptide will be coupled specifically and in a predictable fashion to the carrier (see p. 135, 1st column); hence the use of reagents bearing a maleimide moiety (e.g., MHS, SMCC, and MBS) or activated disulphides (e.g., SPDP), each which couple peptide-carrier conjugates in a predictable manner (p. 135, 2nd and 3rd paragraphs). Peeters reports that compared to anti-peptide antibody titres to the unconjugated peptide, antibody titres were higher when the peptide was coupled to a carrier (in this case, tetanus toxoid) irrespective of the coupling method used (p. 142, 1st column). Finally, Peeters teaches that certain coupling reagents, such as MHS and SPDP, are preferred over SMCC and MBS in terms of their lower potential for immunogenicity, greater flexibility, and greater stability in aqueous solutions (p. 142, 2nd column).

Accordingly, it would have been obvious to one of skill in the art at the time the invention was made to conjugate the chimeric Aβ1-7 peptide to CRM-197 (as discussed above) via chemical crosslinking reagents which conjugate in a predictable fashion, such as, preferably, MHS and SPDP, and also SMCC and MBS, as taught by Peeters et al. The artisan would be motivated to use such reagents because Peeters teaches that conjugation of peptides to carrier proteins using other reagents which conjugate the proteins in a non-predictable manner result in chaotic coupling and products that vary greatly in size and structure. Such variability is undesirable as the "chaotic" immunogenic peptides could elicit the production of antibodies that do not bind to the

desired epitope within Aβ1-7, but instead react with the linker region. The skilled artisan would be further motivated to chemically crosslink Aβ1-7 to CRM-197 using a reagent such as MHS or SPDP because Peeters teaches that such reagents are less immunogenic, more stable, and provide greater flexibility than the other reagents studied whilst still retaining high level of antibody production to the peptide-carrier conjugate. The skilled artisan would therefore reasonably expect that conjugating Aβ1-7 to CRM-197 via chemical crosslinking would result in uniform chimeric peptides which retain high immunogenicity to the desired epitope and not the linker reagent. Thus, the combined references render the claimed invention obvious to the artisan at the time the invention was made.

Claim 133 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/42306 A2 by Chain, as evidenced by Alberts et al., and in view of Frenkel et al., US Patent No. 5,601,827 to Collier et al., and Van den Dobbelsteen et al., as applied to claims 119, 121-124, 126-131, 134-137, and 139-143 above, and further in view of WO 99/10008 by Kensil et al., published 4 March 1999, filed 29 August 1997.

The claims are directed to a pharmaceutical composition comprising Aβ1-7 linked to CRM197 to form a conjugate, said composition also comprising an adjuvant, wherein the adjuvant comprises QS-21.

The teachings of the above combined references are discussed above and teach the use of saponins as adjuvants (see, in particular Chain et al., p. 21, lines 31-33), however, Chain does not specifically teach the use of the saponin adjuvant QS-21.

Kensil et al. teach the use of the adjuvant saponin QS-21 to be employed with vaccines comprising proteins or peptides (see Abstract). Kensil teaches that QS-21 is useful as an immune adjuvant for enhancing immune responses in individuals at a much lower concentration than previously available heterogeneous saponin preparations without the toxic effects associated with crude saponin preparations (p. 1, lines 22-26). Kensil discloses compositions comprising a saponin adjuvant, such as QS-21, an antigen, and an excipient (paragraph spanning pp. 10-11). Kensil teaches that saponins such as QS-21 may be utilized to enhance the immune response to any antigen, such as proteins, peptides, nucleic acids, etc., which may be purified from a natural source, synthesized by means of solid phase synthesis, or obtained by means of recombinant genetics (paragraph spanning pp. 11-12). Kensil also teaches compositions comprising QS-21 that reduce the lytic effect of QS-21 and/or stabilize (increase the half-life of) QS-21 (see Examples 1 and 2, pp. 14-21).

It would have been obvious to one of skill in the art at the time the invention was made to use the adjuvant QS-21, as taught by Kensil et al., in a composition comprising the chimeric Aβ1-7/CRM-197 peptide conjugate (as discussed above) to enhance the immune response to the conjugated peptide. The skilled artisan would be motivated to use QS-21 as an adjuvant because Kensil teaches that QS-21 is useful in vaccine preparations for enhancing immune responses at lower doses and with less toxic side-effects than other crude saponin adjuvant preparations. The skilled artisan would be further motivated to use QS-21 because Kensil teaches QS-21 compositions with significantly improved properties relevant to the lytic effect, tolerance to QS-21

associated pain, and product stability of QS-21, while still maintaining full adjuvant activity. The skilled artisan would therefore reasonably expect that use of the adjuvant QS-21 in a composition further comprising Aβ1-7 linked to CRM-197 would enhance the immunogenicity of the chimeric peptide conjugate. Thus, the combined references render the claimed invention obvious to the artisan at the time the invention was made.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard, Ph.D.
Art Unit 1649
July 31, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER